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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/659,643	09/12/2000	James J. Gibbons Jr.	AM100081	6975

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EXAMINER	
JONES, DWAYNE C	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 04/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/659,643	GIBBONS JR. ET AL.
	Examiner	Art Unit
	Dwayne C Jones	1614

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-7* is/are pending in the application.

4a) Of the above claim(s) *8-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1 and 3-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) *8-14* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/23/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1 and 3-14 are pending.

2. Claims 1 and 3-7 are elected and rejected.

3. Claim 2 was cancelled as per the amendment of December 31, 2003.

4. Claims 8-14 are non-elected and withdrawn from consideration.

Response to Arguments

5. Applicants' arguments filed December 31, 2003 have been fully considered but they are not persuasive. Applicants present the following arguments. First, applicants allege that there is no teaching or suggestion in the reference of U.S. Patent No. 5,545,662 that compounds of formula I can be used as anticancer agents themselves or even that the possess any anticancer properties to suggest combining them with other anticancer agents for purposes of treating solid tumors. Next, applicants allege that although Ayral-Kaloustian et al. teach the formula I compounds are useful in the treatment of cancer, the prior art reference of Ayral-Kaloustian et al. do not teach or imply that the very same anticancer compounds of instant claim 1 as well as the prior art are useful as chemotherapeutic agents.

6. First, applicants allege that there is no teaching or suggestion in the reference of Ayral-Kaloustian et al. of U.S. Patent No. 5,545,662 that compounds of formula I can be used as anticancer agents themselves or even that the possess any anticancer properties to suggest combining them with other anticancer agents for purposes of

treating solid tumors. Instant claim 1 is directed to "[a] method of treating solid tumor in a mammal which comprises administering to said mammal an effective amount of a combination of a cytokine inducer and a chemotherapeutic agent." Ayral-Kaloustian et al. disclose of the administration of urea and urethane compounds of formula I for the treatment of cancer, (see abstract). Ayral-Kaloustian et al. specifically teach the compounds of formula I posses the ability to induce cytokine formation. These teachings could not be clear, and provide blatant motivation, to the skilled artisan to utilize these cytokine inducer compounds of formula I to treat cancer, which inherently includes tumors, namely solid tumors.

7. Next, applicants allege that although Ayral-Kaloustian et al. teach the formula I compounds are useful in the treatment of cancer, the prior art reference of Ayral-Kaloustian et al. do not teach or imply that the very same anticancer compounds of instant claim 1 as well as the prior art are useful as chemotherapeutic agents. In addition, the following definition from Stedman's Medical Dictionary, 25th Edition, Illustrated is provided for the terms chemotherapeutic and chemotherapy, from page 287. Chemotherapeutic relates to chemotherapy. Chemotherapy is the treatment of disease by means of chemical substances or drugs; usually used in reference to neoplastic disease, which is abnormal tissue growth (tumor), (see pages 1029 and 1030). Accordingly, one having ordinary skill in the art would have been motivated to employ "the formula I compounds useful in cancer treatment" (as cited by applicants' appellant in the remarks and amendment of December 31, 2003). Furthermore, applicants instant claim 1 is only directed to administering "a combination of a cytokine

inducer and a chemotherapeutic agent." For this reason, the instant rejection of Ayral-Kaloustian et al. in view of The Merck Index is completely germane to the instant invention, which also teaches "the formula I compounds useful in cancer treatment", (as cited by applicants' appellant in the remarks and amendment of December 31, 2003) and Ayral-Kaloustian et al. specifically disclose the compounds of formula I have the ability to induce cytokine formation, (see column 17, lines 8-10). The instant prior art rejection provides the artisan with the motivation to combine the cytokine inducing compounds of formula I (see column 7, liens 8-10) with well-known chemotherapeutic agents, inter alia bleomycins, cisplatin, mitomycins, vinblastine, and vincristine, as evidenced by the The Merck Index.

8. Due to the above-listed facts and reasons, the remaining rejections of Ayral-Kaloustian et al. in view of The Merck Index under103 based on prior under 35 U.S.C. 102(e) as well as the obviousness-type double patenting rejection for claim 1 is maintained.

Election/Restrictions

9. This application contains claims 8-14 drawn to an invention nonelected with traverse in Paper No. May 12, 2003. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Information Disclosure Statement

10. Because the original copies of the PTO FORM 1449 and the corresponding documents could not be located the examiner respectfully requests copies be furnished of the foreign references as well as the non patent literature, see enclosed copies of the 1449 that were furnished on December 31, 2003.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1 and 3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the cytokine inducer compounds of formula I for the treatment of nonsmall cell type lung tumors with the coadministration with paclitaxel, does not reasonably provide enablement for using other cytokine inducer compounds and for the treatment of other types of tumors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount

of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The instant invention is directed to the cytokine inducer compounds of formula I for the treatment of nonsmall cell type lung tumors with the coadministration with paclitaxel.

(2) The state of the prior art

The compounds of the inventions are the cytokine inducer compounds of formula I for the treatment of nonsmall cell type lung tumors. However, the prior art does not teach that these tumors and cancer are highly unpredictable and consequently their treatment is also highly unpredictable to the artisan, see Stein, J. H.

(3) The relative skill of those in the art

The relative skill of those in the art of pharmaceuticals is high.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements functioning the same in different

circumstances, yielding predictable results, but chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. Supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re Fischer, 427 F.2d 833, 839, 166 USPQ 10, 24 (CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5 (BDAI 1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art; In re Wright, 999 F.2d 1557, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the physiological or pharmaceutical activity of the cytokine inducer compounds of formula I for the treatment of non small cell type lung tumors with the coadministration with paclitaxel prior to filing of the instant invention was an unpredictable art.

(5) The breadth of the claims

The instant claims are very broad. For instance, claim 1 is directed to the plethora of compounds of embraced by the functional description of being known as a

cytokine inducer along with the coadministration of a chemotherapeutic agent. The breadth of claims was a factor in Amgen v. Chugai Pharm. Co., 927 F.2d 1200, 18 USPQ2d (Fed. Cir.),cert. Denied, 502 U.S. 856 (1991). In the Amgen case, the patent claims were directed to DNA sequences that encoded amino acid sequences. Because a very small change in the amino acid sequence of a protein can result in a very large change in the structure-function activity of a protein and because the laws of protein folding are in such a primitive state, predicting protein structure (and hence, activity) while knowing only the sequence of the protein is akin to predicting the weather for a date in the future.

(6) The amount of direction or guidance presented

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fisher, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fischer, 427 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575. In the instant case, given the unpredictability of

the physiological or pharmaceutical activity of a cytokine inducer {state compound} to be effective in treating tumors is insufficient for enablement. The specification provides no guidance, in the way of enablement for cytokine inducer compounds other than those embraced by the compounds of formula I. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S. 5, by Samuel S. Levin covers this subject in detail. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds that fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

(7) The presence or absence of working examples

As stated above, the specification discloses the coadministration of a cytokine inducer and any chemotherapeutic agent and for the treatment of any tumor. However, the instant specification only has enablement for the cytokine inducer compounds of formula I for the treatment of non-small cell type lung tumors with the coadministration with paclitaxel.

(8) The quantity of experimentation necessary

The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in determining whether "undue experimentation" is required to make and use the instant invention. "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all of the compounds that are embraced by the functional description of being known as a cytokine inducer and additionally for the treatment of all tumors with the coadministration of any chemotherapeutic agent that would be enabled in this specification.

13. The rejection of claims 1-3 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because there is insufficient descriptive support for the term/phrase bioresponse modifier and cytokine inducer is withdrawn in response to the amendment of December 31, 2003.

14. The rejection of claims 1-7 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because there is insufficient descriptive support for the phrase "treating solid tumor" is withdrawn in response to the amendment of December 31, 2003.

Claim Rejections - 35 USC § 103

15. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. The rejection of claims 1, and 3-7 under 35 U.S.C. 103(a) as being unpatentable over Ayral-Kaloustian et al. of U.S. Patent No. 5,545,662 in view of The Merck Index is

maintained and repeated for both the above-stated and reasons of record. Ayral-Kaloustian et al. teach the urea and urethane compounds of Formula I are useful in the treatment of cancer, (see abstract). In addition, Ayral-Kaloustian et al. teach that these compounds are useful for their ability to induce cytokine formation and restore bone marrow after chemotherapy, (see column 17, lines 8-10). Ayral-Kaloustian et al. further teach the compounds of Formula I are useful in the treatment of cancer, (see column 19, lines 18-31). The Merck Index teaches of the following known anticancer agents: bleomycins, cisplatin, mitomycins, vinblastine, vincristine, (see pages 183, 329, 890-891, and 427-1428, respectively). The skilled artisan would have been motivated to select any known anticancer agent, such as paclitaxol, to treat cancer especially to obviate multi-drug resistance as well as decrease the toxicity level of a chemotherapeutic agent. Moreover, "[I]t is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . .[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Accordingly, the skilled artisan would have been motivated to combine two pharmaceuticals, which are known to treat the very same ailment, namely cancer, together.

18. The rejection of claims 1 and 3-7 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 5,545,662 in view of The Merck Index is maintained and repeated for both the above-stated and reasons of record.

19. The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2). As cited above in paragraphs 12 and 13.

Obviousness-type Double Patenting

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. The rejection of claims 1 and 3-7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 5,545,662 in view of The Merck Index is maintained and repeated for both the above-stated and reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because U.S. Patent No. 5,545,662 teaches the urea and urethane compounds of Formula I are useful in the treatment of cancer, (see abstract). In addition, U.S. Patent No. 5,545,662 teaches that these compounds are useful for their ability to induce cytokine formation and restore bone marrow after chemotherapy, (see column 17, lines 8-10). U.S. Patent No. 5,545,662 further teaches the compounds of Formula I are useful in the treatment of cancer, (see column 19, lines 18-31). The Merck Index teaches of the following known anticancer agents: bleomycins, cisplatin, mitomycins, vinblastine, vincristine, (see pages 183, 329, 890-891, and 1427-1428, respectively). The skilled artisan would have been motivated to select any known anticancer agent, such as paclitaxol, to treat cancer especially to obviate multi-drug resistance as well as decrease the toxicity level of a chemotherapeutic agent. Moreover, "[I]t is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . .[T]he idea

of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Accordingly, the skilled artisan would have been motivated to combine two pharmaceuticals, which are known to treat the very same ailment, namely cancer, together.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (571) 272-0578. The examiner can normally be reached on Mondays, Tuesdays, Thursday, and Fridays from 8:30 am to 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, may be reached at (571) 272-0584. The official fax No. for correspondence is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

DWAYNE JONES
PRIMARY EXAMINER
Tech. Ctr. 1614
April 3, 2004